Claim Chart demonstrating that claims 1–23, 31-32, and 34-44 of the '741 patent are unpatentable under 35 U.S.C. § 103(a) as obvious over *Ichinose*, *Neonatal Group*, *Macrae*, *Loh*, *Germann* and *Goyal*.

U.S. Pat. No. 8,795,741	*Ichinose*, *Neonatal Group*, *Macrae*, *Loh*, *Germann*, and *Goyal*
CLAIM 1	
A method of treating patients who are candidates for inhaled nitric oxide treatment, which method reduces the risk that inhalation of nitric oxide gas will induce an increase in pulmonary capillary wedge pressure (PCWP) leading to pulmonary edema in neonatal patients with hypoxic respiratory failure, the method comprising:	*Ichinose* teaches that inhaled nitric oxide ("iNO") can be used to treat neonates with hypoxic respiratory failure. ***Safety and Cost-Effectiveness of Inhaled NO in the Newborn*** Large clinical trials have demonstrated that NO inhalation is safe in the hypoxemic term newborn. Inhaled NO has not been associated with clinically evident bleeding in babies with pulmonary disease. In premature babies, studies suggest that inhaled NO does not increase the incidence of intraventricular hemorrhages.[30–33] Several studies indicate that NO inhalation is a cost-effective therapy for treating newborns with hypoxic respiratory failure in part because it decreases the need for ECMO.[34,35] Ex. 1009 at 3108. *Ichinose* teaches that there may be negative effects such as pulmonary edema upon administering iNO to a patient with left ventricular dysfunction ("LVD") and that 20 ppm iNO is a known treatment. Nonetheless, it is important to be aware of the possibility that inhaled NO can produce pulmonary vasodilation and may overwhelm a failing LV, thereby producing pulmonary edema.[79] Ex. 1009 at 3109. Although early studies of inhaled NO in the treatment of pulmonary hypertension used concentrations of 5 to 80 ppm, it has since been realized that concentrations >20 ppm provide little additional hemodynamic benefit in most patients. Ex. 1009 at 3106. At higher inhaled NO_2 doses, pulmonary edema is the major toxicological effect[70] and can result in death.[71] In a simulation using a model lung and commercially available ventilators, production of NO_2 during NO inhalation at 20 ppm appears to be minimal (<0.7 ppm) even with an Fio_2 of 95%.[72] Ex. 1009 at 3109.

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U.S. Pat. No. 8,795,741	*Ichinose*, *Neonatal Group*, *Macrae*, *Loh*, *Germann*, and *Goyal*
	Additionally, *Neonatal Group* teaches term neonates with hypoxic respiratory failure are treated with 20 ppm iNO. ***Methods*** Infants born after a gestation of ≥34 weeks who were 14 days old or less, had no structural heart disease, and required assisted ventilation and whose oxygenation index was 25 or higher on two measurements were eligible for the study. infants were randomly assigned to receive nitric oxide at a concentration of 20 ppm or 100 percent oxygen (as a control). Ex. 1011 at Abstract. Infants born at 34 or more weeks of gestation who required assisted ventilation for hypoxic respiratory failure and had an oxygenation index of at least 25 on two measurements made at least 15 minutes apart were eligible for the trial. Hypoxic respiratory failure was caused by persistent pulmonary hypertension, meconium aspiration, pneumonia or sepsis, respiratory distress syndrome, or suspected pulmonary hypoplasia associated with oligohydramnios and premature rupture of the membranes. [illegible] infants were required to have an indwelling catheter and to undergo echocardiography before randomization. Ex. 1011 at 598. Additionally, *Loh* teaches measuring a baseline wedge pressure prior to administering iNO. (Wedge pressure may also be called pulmonary capillary wedge pressure ("PCWP"), pulmonary arterial wedge pressure ("PAWP"), or merely "wedge." All the terms refer to the same concept). *Loh* further teaches that patients with LVD have a baseline wedge pressure that is greater than 20 mm Hg and that the wedge pressure increases upon treatment with iNO. studied the hemodynamic effects of a 10-minute inhalation of NO (80 ppm) in 19 patients with moderate to severe heart failure secondary to LV dysfunction from idiopathic or ischemic dilated cardiomyopathy. Ex. 1006 at 2780.

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U.S. Pat. No. 8,795,741	*Ichinose*, *Neonatal Group*, *Macrae*, *Loh*, *Germann*, and *Goyal*

To establish baseline conditions, patients inhaled room air (FIO_2, 21%; N_2, 79%) via the closed face mask system for 10 minutes before the baseline hemodynamic measurements. Patients then inhaled NO at 80 ppm (FIO_2, 21%; N_2, 79%)

Ex. 1006 at 2781.

TABLE 1. Hemodynamic Effects of Inhaled NO in Patients With Congestive Heart Failure (n=19)

	Room Air	NO	*P*
HR, bpm	90±3	93±3	NS
MAP, mm Hg	79±3	81±3	NS
SVR, dyne · s · cm^{-5}	1102±104	1041±97	NS
PA, mm Hg	35±4	37±4	NS
PAWP, mm Hg	25±3	31±4	<.001
LVEDP, mm Hg; n=10	28±4	34±5	.02
PVR, dyne · s · cm^{-5}	226±30	119±13	<.001
PA−PAWP, mm Hg	11±1	6±0.5	<.001
SVI, mL/m^2	26±2	24±2	.03
CI, L · min^{-1} · m^{-2}	2.3±0.2	2.1±0.2	.03

HR indicates heart rate; bpm, beats per minute; MAP, mean arterial pressure; SVR, systemic vascular resistance; PA, mean pulmonary artery measure; PAWP, pulmonary artery wedge pressure; LVEDP, left ventricular end-diastolic pressure; PVR, pulmonary vascular resistance; SVI, stroke volume index; and CI, cardiac index.

Ex. 1006 at 2781, Table 1.

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U.S. Pat. No. 8,795,741	*Ichinose*, *Neonatal Group*, *Macrae*, *Loh*, *Germann*, and *Goyal*

Hemodynamic Determinants of an Increase in Pulmonary Artery Wedge Pressure With Inhaled NO

The most prominent hemodynamic effect of NO inhalation was the increase in pulmonary artery wedge pressure (median increase, 26%). In the 10 patients with an increase in pulmonary artery wedge pressure of ≥26% (mean increase, 33±7%), the baseline pulmonary artery pressure, pulmonary vascular resistance, and LV end-diastolic dimension (by M-mode echocardiography; n=16) were higher and the cardiac index and stroke volume index were lower than in the 9 patients with an increase of <26% (Table 2). Thus, more severe LV dysfunction (as evidenced by higher left heart filling pressures, lower stroke volume, and larger LV cavity size) was present in the patients who had the largest increases in pulmonary artery wedge pressure with inhaled NO.

Ex. 1006 at 2782.

TABLE 2. Hemodynamic Characteristics of Patients With a Change in Pulmonary Artery Wedge Pressure Above or Below the Median With Inhalation of NO

	% PAWP <0.26 (n=9)	% PAWP >0.26 (n=10)	P
HR, bpm	87±4	94±3	NS
MAP, mm Hg	75±3	84±3	.02
SVR, dyne · s · cm^{-5}	987±153	1218±148	NS
PA, mm Hg	29±5	42±5	.02
PAWP, mm Hg	21±4	28±4	.02
SVI, mL/m^2	30±2	21±2	.004
CI, L · min^{-1} · m^{-2}	2.6±0.2	1.9±0.2	.01
PVR, dyne · s · cm^{-5}	138±23	295±40	.002
LVEDD, cm	6.2±0.4	7.1±0.3	.04
$\dot{V}O_2$	9.6±0.1	11.7±0.8	NS

LVEDD indicates left ventricular end-diastolic dimension; $\dot{V}O_2$, peak oxygen consumption. Other abbreviations as in Table 1. n=19 for all parameters except EDD (n=16) and $\dot{V}O_2$ (n=17).

Ex. 1006 at 2782, Table 2.

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U.S. Pat. No. 8,795,741	*Ichinose*, *Neonatal Group*, *Macrae*, *Loh*, *Germann*, and *Goyal*
	Goyal teaches that wedge pressure may be measured in infants and children. During cardiac catheterization study, baseline heart rate, systolic, diastolic and mean systemic as well as PA pressures, right atrial pressure and pulmonary capillary wedge pressure (PCWP) were recorded for all the patients Ex. 1007 at 209. **Table 1** Patient characteristics. Data are expressed as median (range) or absolute numbers. BSA, body surface area; Hb, haemoglobin; VSD, ventricular septal defect Age (months) 33 (8–54) M:F 12:7 Weight (kg) 11 (5–17) Height (cm) 89(64–115) BSA (m^2) 0.52 (0.29–0.75) Hb (gm dl^{-1}) 11.2 (10–14) Type of VSD Perimembranous 15 Muscular 2 Multiple muscular 1 Perimembranous with muscular 1 Ex. 1007 at Table 1. *See also* parts (a)-(e)
(a) identifying a plurality of term or near-term neonatal patients who have hypoxic respiratory failure and are candidates for 20 ppm inhaled nitric oxide treatment;	*Ichinose* teaches 20 ppm iNO is a known treatment. Although early studies of inhaled NO in the treatment of pulmonary hypertension used concentrations of 5 to 80 ppm, it has since been realized that concentrations >20 ppm provide little additional hemodynamic benefit in most patients. Ex. 1009 at 3106 At higher inhaled NO_2 doses, pulmonary edema is the major toxicological effect[70] and can result in death.[71] In a simulation using a model lung and commercially available ventilators, production of NO_2 during NO inhalation at 20 ppm appears to be minimal (<0.7 ppm) even with an FiO_2 of 95%.[72] Ex. 1009 at 3109 Additionally, *Neonatal Group* teaches a diagnostic process for

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